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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,734	01/20/2004	Lior Gepstein	27395	7379

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
08/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,734	GEPSTEIN ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-177,182-186 and 196-200* is/are pending in the application.

4a) Of the above claim(s) *1-175 and 182-185* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *176,177,186 and 196-200* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/27/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/13/2009 has been entered.

Applicants' response to the claims filed May 13, 2009 has been received and entered. Claims 178-181and 187-194 and 195 have been canceled, while claim 200 has been newly added. Claims 1-177, 182-186, 196-200 are pending in the application.

Election/Restrictions

Applicant's election of claims 176-195 (group IV) in the reply filed on August 17, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants also elected cardiac specific electrical activity for claims 177 and 189 for first action on merit.

Claims 1-175 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 17, 2006. It is noted that claims 182-185 were drawn to nonelected subject matter. Therefore, claims 182-185 were also withdrawn because they are drawn to non-elected species.

Claims 176-177, 186, 196-199 and 200 drawn to an *in-vitro* culture of isolated human cells that predominantly display at least one characteristic associated with a cardiac phenotype of cardiac specific electrical activity for at least as long as a time period selected from the range of 1-60 days would be examined in the instant application. Claims 176-181, 196-199 and 200 are under examination.

New Matter-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 200 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the recitation of limitation "..consisting essentially of" (claim 200) is considered new matter. Upon further review of the instant specification, examiner could not find support for the term "consisting essentially" in the specification. In fact, example: 1 directly support to an *in vitro* culture comprising human EB comprising mixed population of cystic and non cystic EB. The specification fails to support or define the term "consisting essentially of". MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement". *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed…If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendment made to the disclosure". This is a new matter rejection.

Withdrawn-Claim Rejections- 35 USC § 102

Claims 176-177, 186, 196-199 were rejected under 35 U.S.C. 102 (e) as being anticipated by Funk et al. (US Patent no 6,667,176, dated 12/23/2003, filed on 10/10/2000, effective filing date 6/22/2000).

Applicants arguments filed May 13, 2009 have been fully considered and are persuasive to the extent examiner would agree that EBs disclosed by Funk et al. are subjected to a differentiation period of 11 days, and cells are plated on poly-ornithine coated plates that induces differentiation of cells. It is noted that although EB disclosed by Funk may contain mixed population of cystic and non cystic EB, but Funk fail to teach suspending differentiation by plating human EB on 0.1% gelatin after ~10 days. Therefore, rejection of claims 176-177, 186, 196-199 are hereby withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot.

Claims 176-177, 186, 196-199 were rejected under 35 U.S.C. 102 (e) as being anticipated by Thomson et al. (US Patent no: 7,220,584, dated 5/22/2007, filed on 8/1/2003, effective filing date 2/21/2000).

Applicants provide the reference of Doetschman et al. to support the argument that many cystic structures are present after approximately 11 days of culture of EB (Fig. 3C) and that cardiac lineage cells appear in 30 % of cystic EBs (see abstract and Page 42 bottom). These assertions do not support the fact that there is small percentage of non cytic EB that inherently would show cardiac phenotype. It should be noted that instant application teach only the incidence of spontaneous contraction observed in embryoid bodies derived the H9.2 parental line H9 was about 0.1%. However, applicants' argument that Thomson follows the teaching of Doetschman et al that show cardiac linage appear in EBs that have been cultured in cystic morphology after 11 days is persuasive and therefore, in absence of evidence contrary the rejection is hereby withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot. The claims are however subject to new rejections over the prior art of record, as set forth below.

New-Claim Rejections- 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim interpretation: Clams are directed to an in vitro culture of isolated human embryoid bodies comprising a plurality of non-cystic embryoid bodies each including human cells exhibiting at least one characteristic associated with a cardiac phenotype. As recited instant *in vitro* culture comprises a mixed population of embryoid bodies including cystic as well as non cystic human embryoid bodies (hEB). The instant specification does not provide any specific definition for "consisting essentially of", therefore, the recitation of this term in claim 200 is interpreted as comprising of non cystic EB. MPEP 2111.03 states "For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355".

Claims 176-177, 186, 196-199 and 200 are ejected under 35 U.S.C. 102 (e) as being anticipated by Carpenter et al. (US Patent 7041438, dated 05/09/2006, filed on 10/23/2001, effective filing date 6/22/2000).

Claims are directed to an *in-vitro* culture of isolated human embryoid bodies comprising a plurality of non-cystic embryoid bodies, each including human cells exhibiting at least one characteristic associated with a cardiac phenotype.

With respect to claims 176-177, 186, 196-199 and 200, Carpenter et al. teach an isolated in vitro suspension culture of human embryoid bodies (EBs) that is transferred onto gelatin-coated plates for 4, 8 and 10 days to obtain embryoid bodies comprising beating cells that

exhibits cardiomyocyte phenotype as evident from cardiac troponin I staining (see example 5, col. 48, lines 35-45). It should be noted that Carpenter et al disclose that in some cases more than 75% of the EBs had contracting region (see col. 48, line 43). The cardio specific linage of human cell disclosed by Carpenter et al and those embraced by the instant claims appear to be structurally same, therefore, limitation set forth in claims 177, 186, 196-199 regarding proliferation potential and other cardiac phenotype including electrical activity of these cells will be inherently present in the cells disclosed by Carpenter et al. In the instant case, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Additionally, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, Carpenter et al anticipate claims 176-177, 186, 196-199 and 200.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 176-177, 186, 196-199 were rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. (US Patent no: 7,220,584, dated 5/22/2007, filed on 8/1/2003, effective filing date 2/21/2000), Carpenter et al (US Patent application no 20020137204, dated 09/26/2002, filed on 10/23/2001, effective filing date 6/22/2000) and Igelmund et al (Pflugers Arch. 1999 Apr;437(5):669-79, art of record). It is noted that applicants' argument mainly focus on the reference of Thomson that was applied in conjunction with Carpenter et al and Igelmund

et al. Applicants should note that in the body of the rejection Examiner clearly demonstrated the rationale for one of ordinary skill in the art to substitute mouse EB with human EB comprising non-cystic EB taught by Thomson/ Carpenter et al to arrive to claimed composition. However, Applicant's arguments with respect to the reference of Thomson et al. are persuasive for the reasons discussed in earlier section. Therefore, rejection of claims 176-177, 186, 196-199 is hereby withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot. The claims are however subject to new rejections over the prior art of record, as set forth below.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 176-177, 186, 196-199 and 200 are rejected under 35 U.S.C. 103(a) as being unpatentable over Igelmund et al (Pflugers Arch. 1999 Apr;437(5):669-79, art of record) and Carpenter et al (US Patent application no 20020137204, dated 09/26/2002, filed on 10/23/2001, effective filing date 6/22/2000).

Claim interpreatraThe instant specification does not provide any specific definition for "consisting essentially of", therefore, the recitation of this term in claim 200 is interpreted as comprising of non cystic EB. MPEP 2111.03 states "For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355".

The reference of Carpenter et al is used in instant obviousness rejection to address the limitations of specific characteristics of cardiac phenotype as claimed. It is emphasized that further characterization of known cells using the method of Igelmund et al would have also been obvious to one of ordinary skill in the art.

Igelmund et al teach an *in-vitro* culture of isolated mouse embryoid bodies comprising a plurality of embryoid bodies, each including mouse cells exhibiting at least one characteristic associated with a cardiac phenotype. It is noted that Igelmund et al teach culturing ES cells in suspension culture for 7 days and then plating cells on gelatin coated culture plate for additional 2 to 4 days (7d+2d or 7d+4d) to generate spontaneously contracting cluster of cells (see figure 1 and page 670, col. 1, para.2). It should be noted that EB disclosed by Igelmund et al are generated by culturing human embryonic stem cells for 7 days under non-adherent conditions and then transferring the formed EBs to gelatin-coated plates which froze the formed EBs in a non-differentiated similar to one disclosed for human ES cells in the instant application. Igelmund et al also teach the spontaneous electrical activity of cardiomyocyte clusters in EBs, of small groups of cells, and of single cardiomyocytes (see page 670, col. 1, lines 2-4). The electrode matrix consisted of 60 TiN-coated gold electrodes with a diameter of 10 or 30 μm, arranged in eight columns and eight rows with a distance of 100 or 200 μm between adjacent electrodes (see Figs. 4, 5) (see page 670, column 1, extracellular recording section). Igelmund et al teach that by recording population action potentials from the beating areas of EB, one could determine the electrical interaction between cardiomyocytes and beating activity (see page 677, paragraph 2). Igelmund et al conclude that this potential recordings from clusters of ES cell-derived cardiomyocytes within EBs provide a useful tool for studying in vitro chronotropy and action potential propagation (see page 678, column 1, paragraph 2). However, Igelmund et al do not explicitly teach recording action potential of human cells.

Although, Igelmund et al taught an in vitro suspension culture of embryoid bodies comprising mouse non-cystic EB showing cardiac phenotype, but differ from claimed invention by not explicitly disclosing an *in vitro* culture of human cells.

However, culturing human ES cells in suspension culture for 4-8 days and then plating cells on gelatin coated culture plate to generate spontaneously contracting cluster of human cells was known in prior art. For instance, Carpenter et al teach culturing ES cells in suspension culture for 4-8 days (see para 258) and then plating cells on gelatin coated culture plate for to generate spontaneously contracting cluster of cells (see para.262). It should be noted that spontaneously contracting cells were observed in various regions of the culture until about day

10. It is also disclosed that 100% of the contracting areas were immunoreactive with cardiac troponin indicating the cardiac phenotype of these cells.

Accordingly, in view of the teachings of Igelmund and Carpenter, it would have been obvious for one of ordinary skill in the art to combine the teachings of Igelmund regarding the cardiac phenotype of non-cystic mouse EB with the teachings of Carpenter et al regarding the isolation and suspension culture of human EB to arrive at the claimed composition of an *in vitro* culture of human EB comprising non-cystic EB. One of ordinary skill in the art would be motivated to use human EB comprising non-cystic EB in place of the mouse EB to determine the action potential recordings from clusters of ES cell-derived cardiomyocytes within EBs in order for their potential use in human transplantation medicine. The limitation of wherein at least 20-60% of said human cells exhibit proliferation for at least 1-60 days are implicit characteristics of the cells disclosed by Carpenter et al. One who would practiced the invention would have had reasonable expectation of success because Igelmund et al had already taught the method of extracellular recordings of the population action potentials of cardiomyocyte clusters to perform long-term recordings (for up to several weeks) from individual EBs under cell culture conditions. Carpenter taught human EB containing cardiac linage cells showing cardiac phenotype. Igelmund et al had had already described the use of multiple electrode array system to map the beating area of EBs with electrical activity. Thus, it would have only required routine experimentation to substitute the mouse EB with human EB comprising non-cystic EB containing cardiac cells to determine the action potential of pulsating cardiomyocytes. It is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (<http://www.uspto.gov/web/offices/dcom/bpai/ prec/fd071925.pdf>).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Itskovitz-Eldor et al (Mol Med. 2000 Feb;6(2):88-95, IDS) teach presence of non-cystic EB in human ES cells (see figure 1A ii-iii).

Stuhlmann et al. (US Patent application 20020023277, dated 02/21/2002, filed on 5/22/1998) teach an in vitro culture of mouse ES cell clumps containing "simple "EBs" that is kept for another six days in suspension culture, where they further differentiated into complex "cystic EB" containing visible cavitation pockets of rhythmically contracted cardiomyocytes meeting the limitation of the claim. It is noted that cystic EB with cavitation is interpreted as non-cystic EB. It is also disclosed that 4 days suspension culture of EB are also re-plated on gelatinized tissue culture plates containing contracting cardiomyocytes, differentiated cell types with an uncharacterized phenotype, as well as pockets of undifferentiated cells, was observed during the next six days. It should be noted that Stuhlmann et al. analyzed EB of at day 4, day 7 and day 10 in suspension culture.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632